

The Effect of Modafinil on Behavioural and ERP Measures of Attention and Associated Sex
Differences

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Statement of Sources

I declare that this report is my own original work and that contributions of others
have been duly acknowledged

Date:_____

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Abstract

Modafinil is a wakefulness-promoting drug that is becoming more commonly used for off-label for attentional enhancement in healthy individuals despite conflicting evidence to support this. The aim of the current study was to investigate the effects of modafinil on behavioural (reaction time & accuracy) and ERP (N1 amplitude) measures of the attentional alerting and orienting networks and also investigate any sex differences associated with these effects. The final sample consisted of 14 females and 22 males who were all healthy and met the screening criteria. Each participant completed two sessions differing by drug condition (200mg modafinil or placebo). The Attentional Network Task was used to assess the effects on both the alerting and orienting network and this task was completed at baseline and at 2.5 hours post-ingestion. As expected, reaction time decreased and N1 amplitude increased as cues became more informative. There was a small enhancement of the alerting network demonstrated by a significant decrease in reaction time from baseline to post-ingestion for central cues in the modafinil condition but not placebo. There was a small significant decrease in reaction time from baseline to post-ingestion for spatial cues but this is likely due to alerting enhancement rather than orienting as the effects were of similar size. Inconsistent to the hypotheses, males had a faster reaction time to all cue types when compared to females. Males also showed greater N1 amplitude after modafinil ingestion than placebo, indicating some sex differences in the effect of modafinil may be present. These results suggest that modafinil may have an enhancing effect on the alerting network but not the orienting network. The effects of modafinil on the orienting network has not been well studied so future research is required to confirm this finding. There also appears to be differential effects of modafinil on males and females, which also requires future investigation as this is the first study to look at these effects.

Modafinil is a schedule IV drug labelled as a psychostimulant for its wakefulness promoting properties (Minzenburg & Carter, 2008). It is most commonly used to treat excessive daytime sleepiness in narcolepsy, shift work disorder and obstructive sleep apnoea. However, it is becoming more commonly used off-label for a variety of other conditions including attention-deficit/hyperactivity disorder (ADHD) and depression.

Modafinil has also been evaluated for cognitive enhancement (including attention) in healthy individuals. Petersen and Posner (2012) suggest three main networks of attention, alerting, orienting and executive control. Findings into the effects of modafinil on these networks have been inconsistent. When methodological issues are accounted for (task complexity), there are consistent findings of alerting network enhancement after modafinil ingestion, but only for complex task paradigms (Battleday & Brem, 2015). The orienting network has not been extensively studied, with only one study using a task that could analyse orienting (Ikeda, Funayama, Tateno, Fukayama, Okubo, & Suzuki, 2017). This study did not find any orienting enhancement after modafinil ingestion, but further research is required into the effect of modafinil on this network. Similarly to the alerting network, research suggests that more complex task paradigms (including inhibitory control processes) are required to detect enhancement after modafinil in executive control components of attention (Battleday & Brem, 2015).

There is evidence that males and females differ in the attentional networks. Specifically, females appear to be better at orienting their attention (orienting network) and responding to valid cues while males show less costs to invalid cues (Liu, Hu, Fan, Wang, 2013; Merritt, Hirshman, Wharton, Stangl, Devlin & Lenz, 2007). With regards to Event-Related Potential (ERP) indices of attentional processes, females have shown greater N1 amplitude while completing orienting based tasks than males. However, no study is yet to investigate the differing effects of modafinil on males and females attentional processing.

Most studies examining the effects of modafinil have recruited exclusively male participants, while studies that do incorporate females have failed to analyse for any sex differences. Therefore, this study aims to investigate the effects of modafinil on both males and females attention, by using an attentional network task to specifically assess Petersen and Posner (2012)'s alerting and orienting networks.

Neurochemical Effects of Modafinil

Modafinil is a wakefulness-promoting agent primarily prescribed for the treatment of narcolepsy and excessive daytime sleepiness, but is becoming more commonly used for other conditions (Minzenburg & Carter, 2008). It is a psychostimulant, but has been found to contain a different structure to other amphetamines. Modafinil has various effects on the catecholamine system, including reuptake inhibition of dopamine and norepinephrine as well as increased levels of serotonin, glutamate and catecholamine and decreased GABA. Dopamine receptors are thought to be crucial for the arousal and wakefulness effects of modafinil (Qu, Huang, Xu, Matsumoto & Urade, 2008), as are the effects on the catecholamine systems (Minzenburg & Carter, 2008).

The Attentional Networks

Attention is an important aspect of cognitive functioning as it allows the brain to sift through vast amounts of information that is received through the senses (Einothar & Guesbrecht, 2013). Petersen and Posner's (2012) attentional model outlines three separate but interacting networks of attention, alerting, orienting and executive control.

The alerting network is involved in maintaining arousal and vigilance when completing a task (Petersen & Posner, 2012). To analyse the alerting network, a warning signal is produced prior to the onset of the target, which replaces the resting state with a state of readiness for the target to appear. This measures phasic alertness. Another way to measure alerting is to use a long task to measure sustained vigilance or tonic alertness. The alerting

network primarily relies on the neurotransmitter norepinephrine (Petersen & Posner, 2012). The brain areas involved include the locus coeruleus, as well as regions of the frontal and parietal cortices. As norepinephrine is increased in the brain after modafinil ingestion (Petersen & Posner, 2012), it could be expected to enhance the alerting network.

The orienting network is involved in prioritising certain sensory information by selecting it amongst other sensory information (Petersen & Posner, 2012). The frontal and parietal areas are primarily involved in the orienting network. There are two brain systems relating to the orienting network, a dorsal system and a ventral system (Vossel, Geng & Fink, 2014). The dorsal system is comprised of the intraparietal sulcus and the frontal eye fields of each hemisphere, which are organised retinotopically. The dorsal system is active when attention is covertly or overtly oriented in space, such as after a predictive spatial cue. The ventral system is made up of the temporoparietal junction and the ventral frontal cortex. This system is activated when stimuli appear in an unexpected location such as when an invalid cue is presented and is involved in disengaging attention from the current location.

The executive control network is involved in higher order processes including selective attention and monitoring of stimuli (Petersen & Posner, 2012). This network consists largely of the anterior cingulate cortex and frontal brain areas. The primary neurotransmitter is the dopamine neurotransmitter. Executive control relies on top down control processes and performance guidance signals. As dopamine is increased by modafinil, it could be expected to enhance the executive control network.

The Attentional Network Task

The attentional network task is a paradigm designed to analyse the alerting, orienting and executive control networks (Fan, McCandliss, Sommer, Raz & Posner, 2002). In the task, one of three different cue types is presented before the target appears. These are no cue (continue to see fixation cross), a central cue (cue appears over fixation cross) and a spatial

cue (cue appears either above or below the fixation cross). The central cue is thought to activate the alerting network, as a state of alertness is elicited by the cue. The spatial cue is always valid (appears at the same location as the target) and activates the orienting network, as the cue guides the participant's attention to the location the target will appear. The target is an arrow (appearing above or below fixation), facing to the left or the right, which is accompanied by four flanker arrows, two on each side. The flanker arrows are either congruent (facing the same way as the target) or incongruent (facing the opposite way to the target). These flanker arrows assess the executive control network, as incongruent arrows must be inhibited to respond to the target, which is facing the opposite way. Participants respond to the direction of the centre arrow by pressing the corresponding button.

Neuhaus et al. (2010) investigated the alerting, orienting and executive control networks using the attentional network task. The results indicate that reaction time was significantly faster following central cues than no cue, which indicates activation of the alerting network. Reaction time was also significantly faster following spatial cues relative to central cues, which indicates activation of the orienting network.

Electrophysiological correlates of the ANT

Event-related potentials (ERPs) involve placing electrodes on the scalp to record brain activity and then averaging that activity to a specific target (Luck, 2014). ERPs can be used to determine specific neural mechanisms of attention. The visual N1 component peaks approximately 150ms post stimulus and is influenced by spatial attention. The N1 component appears larger (more negative) when participants are required to discriminate between stimuli than when they are merely required to detect the presence of a stimulus (Vogel & Luck, 2000). The N1 component is greater when the spatial scale of attention is more focussed (e.g. smaller cues) (Matthews, & Martin, 2015).

Neuhaus et al (2010) also analysed the target locked N1 component following each cue type in the attentional network task. The results showed that N1 amplitude was significantly greater for central cues compared to no cues. N1 amplitude was also significantly greater following spatial cues relative to central cues. This indicates that the N1 component becomes greater (more negative) as cues become more informative.

Sex Differences and Attentional Networks

The research into sex differences in the attentional networks has produced mixed findings. Consistently, there have been no significant differences found between males and females for the alerting and executive control networks (Liu et al. 2013; Neuhaus et al. 2009; Xiao et al. 2016). The findings for the orienting network are more inconclusive, with some studies reporting differences between males and females and others reporting no difference.

Several studies have used an attentional network task to examine sex differences for the orienting network. Liu et al. (2013) used this paradigm and their results showed an increased orienting effect in females when compared to males. This result indicated that females were better at orienting their attention to the target than males. Another study used the attentional network task to determine any sex differences in the orienting network (Xiao et al., 2016). This study reported no significant differences between males and females for spatial cues, indicating no difference in the orienting network between the sexes. There were also no significant differences in alerting or executive control between females and males.

Neuhaus et al. (2009) also used an attentional network task to see if any sex differences are present in the orienting network. This study used reaction time measures as well as event related potentials, including the N1 component. The results showed a trend towards males having a faster reaction time, but this difference was not significant. However, there was a significant difference in the N1 component for spatially cued trials between the

sexes. Females showed a second N1 component peak, which resulted in greater N1 activity in females than in males.

An additional study used a spatial cuing paradigm to analyse sex differences in the orienting network (Merritt et al. 2007). This task required participants to respond to a target that appeared in one of four boxes on the screen. Some targets were preceded by cues, some were valid and some were invalid. The findings showed that males had a reduced overall reaction time when compared to females. More specifically, males showed a benefit from the invalid cues compared to the no cue control trials, while females showed benefit from the valid cues. As cues in the attentional network task are always valid, this finding could be consistent with the results of Liu et al. (2013), such that females indicated an increased orienting effect when compared to males. As females were found to benefit from valid cues, this could indicate why females were found to be better with spatial cues on the attentional network task.

The research into sex differences in the attentional networks has produced mixed results. Consistently, no effect has been found for either the alerting or executive control networks. However, the research is inconsistent into the differences between males and females for the orienting network. Significant findings suggest that females perform better on orienting tasks than males and also have greater N1 amplitude, however, more research is needed to corroborate these findings. There is currently no research into the effect of modafinil on these sex differences.

Modafinil and Attention

Repantis, Schlattmann, Laisney and Heuser (2010) conducted a review of the literature surrounding the effect of modafinil on attentional processes in healthy non-sleep deprived individuals. The review included 25 previous articles that specifically used modafinil to investigate the effects on attention. In studies where modafinil was only

administered once, non-sleep deprived individuals showed a moderate positive improvement in attention following modafinil ingestion ($d=0.56$). The tasks employed by the reviewed studies primarily assessed the alerting network (reaction time tasks, digit detection tasks, rapid visual information processing task). The executive control network could not be analysed in this review due to the lack of baseline data.

Battleday and Brem (2015) conducted a later review of the literature concerning modafinil and attention in healthy individuals. This review included 24 studies. The results found no consistent improvement to simple attention tasks (reaction time tasks, Rapid Visual Information Processing Task) following modafinil. However, when more complex tasks were used to analyse attention, more consistent improvements are observed. These tasks primarily assessed more than one cognitive domain (learning task involving attention, decision making based on spatial targets). The inconsistent results for studies using simple tasks could be due to those tasks lacking the sensitivity to detect any attentional differences in healthy non-sleep deprived individuals. Therefore, it is suggested that more complex tasks should be used when assessing healthy individuals to address the ceiling effects observed for simple tasks.

Battleday and Brem (2015) found enhancement of inhibitory control in studies that used a more complex task. The findings into the effects of modafinil on executive functions for simple tasks are inconsistent, with some studies reporting significant differences and others reporting null findings. This suggests that more complex tasks (tasks presenting stimuli visually and auditory simultaneously) may be necessary to detect enhancement of inhibitory control after modafinil ingestion.

The Alerting Network and Modafinil

The research into the effects of modafinil on the alerting network has produced varying results. These inconsistencies could be due to the methodological issues, mainly ceiling effects that have been identified when simple tasks are used to assess the alerting

network (Battleday & Brem, 2015). Turner et al. (2003) used the RVIP to assess sustained attention. This task was part of a larger cognitive battery. The RVIP involves detecting a series of three digits from a sequence of consecutively presented digits. Sixty participants were allocated to either a placebo, 100mg modafinil or 200mg modafinil condition and completed the cognitive battery two hours post drug ingestion. The results indicated no difference between any of the conditions in their reaction time, suggesting no enhancement of the alerting network.

Randall, Shneerson and File (2005) also used the RVIP to assess sustained attention. Eighty-nine healthy non-sleep deprived participants completed one session where they received either 100mg modafinil, 200mg modafinil or a placebo. Participants were also split into low IQ and high IQ groups using their scores on the National Adult Reading Test-II. The RVIP was part of a larger cognitive battery and was completed 2-3 hours post-ingestion. The results showed modafinil significantly decreased the number of missed targets. Target sensitivity was significantly higher in both modafinil conditions but this was only present in the low IQ group. These results suggest that in high IQ samples, some tasks may not be sensitive enough to detect the effects of modafinil.

Liepert, Allstadt-Schmitz, and Weiller (2004) used a reaction time task that evoked both phasic and tonic alertness to investigate the effect of modafinil on the alerting network. Ten male participants completed two sessions at least two weeks apart where they either ingested 200mg modafinil or placebo. For each session testing occurred 1 hour prior to ingestion, 2-3 hours after ingestion, and 24 hours later. The reaction time task involved a visual go-signal in which the participants responded by pressing a button (tonic alertness). Some trials were preceded by an auditory warning signal (phasic alertness). While the reaction time was generally faster for trials with the warning cue than those without, there was no significant difference between conditions on their reaction times for the task. These

results indicate no enhancement of the alerting network after modafinil ingestion. This could be because the task used in this study along with the RVIP used by Turner et al. (2003) and Randall et al. (2005) were not sensitive enough to detect a difference between the modafinil and placebo groups in a healthy non-sleep deprived population.

Theunissen et al. (2009) used a more complex task to assess the alerting network after modafinil ingestion. A sustained attention Mackworth clock test was used which includes a clockwise sequence of dots that light up. Participants have to respond by pressing a button when one of the dots was missed in the sequence. Sixteen participants (11 female) completed two sessions, one 200mg modafinil session and one placebo session. The clock test was completed as part of an array of other tasks and testing occurred two hours after ingestion. Reaction time was significantly lower in the modafinil condition when compared to placebo, indicating that modafinil enhanced the alerting network. There was no treatment effect on accuracy.

Cope et al. (2017) investigated the effects of a single dose of modafinil (200mg, 400mg or placebo) on the alerting network. Sixty healthy participants were allocated to one of the three conditions where they completed the 5-choice continuous performance task after drug ingestion. The task involved participants moving a joystick in the direction of a white dot that appeared behind one of five white lines, or not responding if dots appeared behind all of the five white lines (no-go trials). Both doses of modafinil enhanced performance on this task. The improvement in this task was possibly a result of more targets detected by both modafinil doses than placebo, leading to higher accuracy. This suggests that modafinil enhanced the alerting network by increased ability to detect targets in the task.

Baranski, Pigeau, Dinich, and Jacobs (2004) assessed the effects of modafinil on the alerting network as part of a larger cognitive battery. Eighteen male participants completed testing at three time points throughout each session (90 minutes prior to ingestion, 90 minutes

after ingestion and three hours after ingestion). Two sessions were completed and differed by drug condition, 4mg/kg of modafinil or placebo. The detection of repeated numbers task was used to measure sustained attention. The task consists of three numbers presented on a screen simultaneously, and requires participants to respond when the same three-digit sequence occurs twice in a row. Modafinil resulted in increased vigilance on the task but it was due to more targets being detected in the modafinil condition, leading to a higher accuracy. This is consistent with the findings by Cope et al. (2017) where modafinil ingestion resulted in increased accuracy when compared with placebo.

Ikeda et al. (2017) assessed the alerting network using an attentional network task. The task was adapted for use with fMRI so brain activation could be analysed. The study included 23 participants (14 male) who each completed two sessions at least two weeks apart in which they completed both a placebo and 200mg modafinil. The participants completed the attentional network task at 2.5 hours post drug ingestion. The reaction time for the modafinil condition was significantly faster for central cue trials when compared with the placebo condition, indicating enhancement of the alerting network. The alerting effect was calculated by subtracting the mean reaction time for the central cue trials from the mean reaction time for the no cue trials, which produced no treatment difference of the alerting effect between modafinil and placebo conditions. The accuracy of the task was higher in the modafinil condition. For fMRI analyses, the modafinil condition showed significantly more activation in certain areas, particularly the occipital gyri, than the placebo condition. These results suggest that the alerting network was enhanced after modafinil ingestion.

In summary, when more complex tasks (clock test, detection of repeated numbers, attentional network task) are used to investigate the effects of modafinil on the alerting network the results are more consistent. These tasks appear to be more sensitive in detecting differences between modafinil and placebo conditions in healthy populations (Baranski et al.

2004; Cope et al. 2017; Ikeda et al. 2017; Theunissen et al. 2009). The same result could be expected in the present study, using an attentional network task to investigate the effect of modafinil on the alerting network. If consistent with these studies, the alerting network should be enhanced after modafinil ingestion.

The Orienting Network and Modafinil

There is currently only one study that has investigated the effects of modafinil on the orienting network. As mentioned above, Ikeda et al. (2017) used an attentional network task to investigate the effect of 200mg of modafinil as well as a placebo dose on the orienting network. The task was adapted for use with fMRI. The behavioural results were obtained by subtracting mean reaction time for the spatial cue trials from the mean reaction time for the central cue trials. This showed that modafinil did not enhance the orienting network when compared with the placebo condition. However, the accuracy for the task was higher in the modafinil condition when compared with the placebo condition. There were no significant differences in brain activation between the modafinil and placebo conditions as shown by the fMRI analyses. These results suggest that modafinil does not enhance the orienting network. The same result could be expected for the orienting network in a study using the same dose of modafinil and also an attentional network task.

Aim, and Hypotheses

There are currently no studies that investigate the differential effect of modafinil on attentional processing of males and females. This study aims to address this gap in the literature by recruiting both male and female participants and directly analysing for any sex differences after modafinil ingestion compared to placebo. There are also no studies that use ERP measures to investigate the effect of modafinil on the N1 component. This study will include the N1 component as a dependent measure to address this.

The aim of this study is to investigate the effect of 200mg modafinil on attentional alerting and orienting networks and investigate any sex differences associated with these effects. The executive control network will not be analysed as it is out of the scope of this thesis. Reaction time, accuracy and N1 amplitude will be the dependent measures used.

Consistent with Neuhaus et al. (2010) it is hypothesised that reaction time will be significantly shorter following central cue trials than no cue trials. Reaction time should also be significantly shorter following spatial cue trials than central cue trials. As it is expected that modafinil will enhance the alerting network, the difference in reaction time between the central cued trials and the no cued trials should be greater in the modafinil condition compared to the placebo condition. It is not expected that modafinil will enhance the orienting network, therefore the difference in reaction time between the spatial cued trials and the central cued trials will not be significantly different for the modafinil and placebo conditions.

The N1 component is expected to be significantly larger (more negative) following central cue trials than no cue trials. The N1 will also be significantly greater following spatial cue trials compared to central cue trials. As alerting enhancement after modafinil is expected, the difference in N1 amplitude between the central cued trials and the no cued trials will be larger in the modafinil condition compared to the placebo condition. As no orienting enhancement is expected, the difference in N1 amplitude between the spatially cued trials and the central cued trials will be consistent for both the modafinil and placebo conditions.

It is not expected that reaction time or N1 amplitude will be significantly different for male and females following central cue trials or no cued trials. Therefore, it is not expected that males and females will show any significant differences in these measures after modafinil ingestion. Consistent with findings by Liu et al. (2013) it is expected that females will have a significantly faster reaction time following spatial cues than males. Females will

also show greater N1 amplitude following spatial cues than males. As it is not expected that modafinil will directly influence the orienting network, males and females should not differ significantly between the modafinil and placebo doses.

Method

Participants

An a priori power analysis indicated that 20 participants per group would be required to detect a moderate effect ($f=0.25$) with a power of 0.8. The final sample consisted of 14 females and 22 males aged 18-30 ($M=21.38$, $SD=2.89$). Recruitment occurred through the university resources and via social media. Participants were excluded if they smoked nicotine, frequently used illicit drugs, were not in the 18-30 age range or were taking any medications. Participants were also excluded if they were at high risk of alcohol dependence, identified by scores >16 on the Alcohol Use and Disorders Identification Test (AUDIT) (Babor, Higgins-Biddle, Saunders & Monteiro, 2001). Participants were excluded if they were at high risk of psychological distress as measured by scores <30 on the Kessler Psychological Distress Scale (K10) (Andrews & Slade, 2001) or if they were at risk of psychosis as measured by scores >1 on the Psychosis Screener (Degenhardt, Hall, Korten, Jablensky, 2005) and scores >17 on the Schizotypal Personality Questionnaire-Brief (Raine & Benishay, 1995). Participants received \$80 as reimbursement for their time and first year psychology students could receive 4 hours course credit and \$40.

Materials and Apparatus

Screening Questionnaires

The Alcohol Use and Disorders Identification Test (AUDIT). The AUDIT is a measure of alcohol abuse and dependence (Babor et al. 2001). It is comprised of three items

assessing hazardous alcohol use, three items assessing dependence symptoms of alcohol and four questions assessing harmful alcohol use. The first eight questions are responded to on a five-point scale and the last two are on a three-point scale. Scores greater than 16 are indicative of problematic alcohol use or dependence.

The Kessler Psychological Distress Scale (K10). The K10 is a measure of global psychological distress (Andrews & Slade 2001). The scale is comprised of ten questions about how the individual has been feeling over the past four weeks. Response is on a five-point scale from 1 (none of the time) to 5 (all of the time). Scores higher than 30 are considered to be at high risk of psychological distress.

Psychosis Screener. The psychosis screener consists of four items plus three sub-items that measure an individual's risk for psychosis (Degenhardt et al. 2005). The questions are related to the main symptoms experienced by those with psychosis and are responded to with either a yes or no answer.

Schizotypal Personality Questionnaire-Brief (SPQ-B). The SPQ-B consists of 22 items that measure for schizotypal personality traits (Raine & Benishay, 1995). Items are answered either true or false and fall within three categories (cognitive-perceptual, disorganised and interpersonal). Scores >17 indicate high schizotypy.

Demographic Questionnaires

The Wechsler Test of Adult Reading (WTAR). The WTAR is a measure of verbal intelligence (Green et al. 2008). It is made up of fifty irregular words that the participant is asked to read aloud. For each correct word, a point is given, with higher scores indicating higher intelligence. Raw scores can then be converted to standard scores to give an estimate of verbal IQ.

Wakefulness and Affect Measures

Karolinska Sleepiness Scale (KSS). The KSS is a measure of present fatigue and sleepiness (Akerstedt & Gillberg, 1990). Participants rate their fatigue on a nine-point scale ranging from 1 (extremely alert) to 9 (very sleepy, fighting sleep).

Profile of Mood States- Short Form (POMS-SF). The POMS-SF is a measure of subjective mood (Shacham, 1983). It is comprised of 37 different mood states, which participants rate for their present feeling of that state. Responses are given on a five-point scale, ranging from 0 (not at all) to 4 (extremely).

Visual Analogue Scales (VAS). VAS were used as measures of subjective performance and subjective drug effects. The VAS comprised of four statements regarding perceived performance at the present time and four statements regarding feeling the effects of the drug at the present time. Participants mark the point on a 10cm line that most accurately describes their experience at the time from ‘strongly agree’ to ‘strongly disagree’. The line was measured and converted to a percentage out of 100%. VAS subjective performance statements included alertness, ability to perform tasks, impaired driving, and capacity to drive safely at the time. For statements about subjective drug effects, statements related to liking of the drug, strength of the drug, alert level and intoxication.

Attentional Network Task

The attentional network task was based on the version developed by Fan et al. (2002) (See Figure 1). The task began with ten practice trials. The baseline task consisted of 192 trials that lasted approximately 10 minutes in total. The experimental task consisted of 586 trials that were randomly generated lasting approximately 35 minutes. Instructions appeared on the screen prior to the start of the task that indicated what should be responded to, and which buttons to press. A white fixation cross appeared on the screen throughout the duration of the task. The task begins with 400ms of fixation, followed by presentation of one of three

cue types for 100ms. For the central cue, the cue appeared over the fixation cross. For the spatial cue, the cue appeared 1.01 degrees either above or below the fixation cross. Spatial cues were always valid and indicated the location that the target would appear. After the cue, the target was presented. This was an arrow, which was facing either to the left or the right. The target arrow was accompanied by four flanker arrows, two on each side, which were either congruent (>>>>) or incongruent (<<<<) with the target arrow. The participant's task was to respond to the direction of the target arrow by pressing the corresponding button as quickly and accurately as possible. The response was collected between 150-1500ms after the target was presented. The task had four inter-trial intervals, 1,300ms, 1,200ms, 1,100ms and 1,000ms.

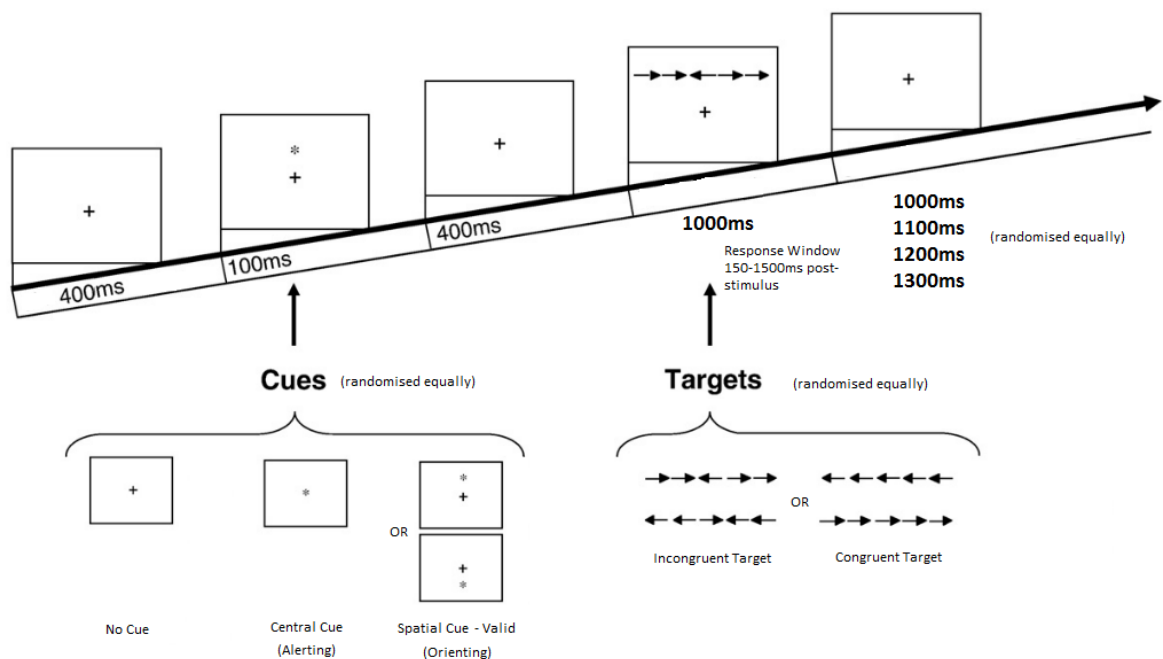


Figure 1. An Illustration of the Attentional Network Task

Electrophysiological Recording

A NeuroSCAN system and a 32-channel Quik cap was used to record electrophysiological (EEG) activity. EEG data was recorded continuously from 32 electrode sites using the 10-20 system of electrode placement. Electrodes were referenced to the

mastoids and impedance was kept below 10k Ω . Electro-oculographic activity was recorded horizontally from electrodes placed outside the eyes and vertically with electrodes placed above and below the eye.

The behavioural and ERP data were merged together for editing. Data was filtered through a low pass filter (30Hz, 24dB/Oct). Ocular artefact reduction was used to reduce interference from eye blinks. Epochs were extracted from -100-900ms post stimulus and an artefact rejection procedure was applied at \pm 70 microvolts.

Procedure

The University of Tasmania Health and Medical Human Research Ethics Committee approved the study (H0011386, Appendix A). Participants gave informed consent before beginning their first session (Appendix B, C & D). Screening interviews were conducted over the phone and consisted of questions relating to age, previous illicit drug use, medical history and smoking status as well as short versions of the AUDIT and the Psychosis Screener (Appendix E). Additional screening questions were completed at the beginning of the first session and included the full AUDIT, K10 and SPQ-B (Appendix F).

Eligible participants completed two four-hour sessions that were at least a week apart to ensure no lasting effect of modafinil. These sessions differed by drug condition (200mg modafinil or placebo capsules made with cornflour). This was double-blind and randomised. All sessions began at either 12 or 1pm. Participants were instructed to abstain from alcohol 24 hours prior to each session, maintain normal caffeine intake, abstain from paracetamol/ibuprofen on the day and eat a light meal before the session. Researchers were first aid trained in case of any adverse reactions to the modafinil.

At the beginning of session 1, participants completed demographic questions as well as the full AUDIT, K10, SPQ-B and WTAR. For both sessions, participants completed questionnaires relating to food and caffeine intake for that day as well as the POMS-SF, KSS

and VAS for subjective performance (Appendix F). Pre-ingestion, participants completed the baseline versions of two tasks (25 minutes total), including the ANT. Participants then consumed the capsules and waited for approximately 2 hours. They were then set up for electrophysiological recording and were ready to complete the full experimental tasks, including the ANT at 2.5 post-ingestion. These tasks lasted a combined total of 45 minutes and order was counterbalanced across participants. After completing both tasks, participants completed additional questionnaire measures (POMS-SF, KSS, and both VAS measures). Participants also indicated as a percentage the likelihood that they believed they had ingested the modafinil capsules in the current session. The second session followed the same design as the first, only differing in capsule content. At the end of the second session, participants were debriefed, thanked for their time and reimbursed with AUD\$80 or a combination of cash and course credit (for first year psychology students).

Design and Data Analysis

Two separate 3x2x2x2 repeated measures ANOVAs were conducted to examine the effects of Cue (no, central, spatial), Drug (modafinil or placebo), Time (baseline or post-ingestion) and Sex (female, male) on reaction time and accuracy. As congruency was not of particular interest to the current study, the data was averaged across congruent and incongruent trials. Pairwise comparisons were used to follow up significant interactions. Non-significant interactions that were relevant to the hypotheses were followed up with hypothesis driven planned comparisons.

The dependent measure of N1 amplitude was maximal at electrode site OZ as determined by preliminary analyses, and all further analyses were restricted to this electrode site. A third 3x2x2 repeated measures ANOVA was conducted with the variable of Time removed, as ERP data was only collected post-ingestion. Similarly, significant interactions

were followed up with pairwise comparisons and any hypothesis related interactions were followed up with hypothesis driven planned comparisons.

Paired-samples t-tests were used to determine any differences in control variables at baseline for each session (caffeine, sleep hours, fatigue, alertness). Paired-sample t-tests were also used to measure whether VAS subjective drug effects (alertness, liking of drug, strength of drug and intoxication) differed at post-ingestion between drug conditions.

Four 2x2x2 repeated measures ANOVAs were used to analyse the effect of Time, Drug and Sex on VAS subjective performance ratings (alertness, task ability, impaired driving and drive safely). Six 2x2x2 repeated measures ANOVAs were conducted for each POMS subscale (total, depression-dejection, vigour-activity, fatigue-inertia, tension-anxiety, anger-hostility and confusion-bewilderment) by Drug, Time and Sex. A 2x2x2 repeated measures ANOVA was conducted for the KSS by Drug, Time and Sex.

For all main effects and interactions involving the variable Cue, sphericity was not assumed as there are three levels and therefore a Greenhouse-Geisser correction was made for all the relevant analyses. Partial eta squared was used to quantify effect sizes for all ANOVAs and Hedge's *g* was used to aid in the interpretation of any planned comparisons and was interpreted using Cohen's (1992) guidelines, small (0.2), moderate (0.5) and large (0.8).

Results

Demographic and Screening Measures

Participants scored within the cut off limits on all screening variables, with no one displaying any problematic alcohol use, risk of psychosis or risk of psychological distress (Table 1). All participants had completed to at least year 10 and most were enrolled at University (79.1%) at time of testing. BMI was within the normal range and mean intelligence was above average for this age group.

Table 1

Means for Demographic and Screening Variables

Variable	Female		Male	
	<i>M (SD)</i>	Range	<i>M (SD)</i>	Range
Age	21.25 (3.57)	19-30	21.46 (2.54)	19-27
K10	12.13 (3.25)	5-18	12.67 (4.53)	8-23
AUDIT	6.40 (4.30)	0-15	4.05 (2.80)	0-10
WTAR (standard score)	112.00 (10.45)	87-124	104.50 (9.72)	80-119
BMI	24.99 (3.48)	17-31	23.01 (3.88)	18-34

Manipulation Check

A paired samples t-test revealed that participants were more sure that they had taken modafinil in the modafinil condition ($M=55.54$, $SD=34.49$) than the placebo condition ($M=28.24$, $SD=30.09$), $t(34)= 3.76$, $p=.001$, $g=0.83$.

Baseline

A series of paired sample t-tests revealed that participants did not differ significantly at the baseline of each session for possible confounding variables (Table 2). Participants did not differ in the number of caffeinated beverages consumed before each session and hours of sleep were consistent across both sessions. Baseline reports of fatigue (KSS), Alertness (VAS) and mood (POMS) were not significantly different across sessions.

Table 2

Means (SD) & t-test results for Baseline Measures

	Modafinil	Placebo	<i>t</i>	<i>p</i>	<i>g</i>
Caffeine Intake	0.68 (0.82)	0.65 (0.72)	0.27	.786	0.04
Sleep (hours)	7.61 (1.10)	7.88 (1.13)	-1.44	.158	-0.24
Fatigue (KSS)	4.41 (1.52)	4.32 (1.40)	0.36	.723	0.06
Alertness (VAS)	32.39 (13.53)	34.53 (17.30)	-0.94	.353	-0.14
Total Mood	12.81 (9.14)	13.03 (8.31)	-0.20	.842	-0.03
Disturbance (POMS)					

Mood and Fatigue

There were significant Time x Drug interactions for the depression-dejection, vigour-activity and fatigue-inertia subscales of the POMS (Tables 3 & 4). Planned comparisons revealed depression-dejection was significantly decreased from baseline to post-ingestion in the modafinil condition ($p=.003$, $g=0.69$). Fatigue-inertia was significantly higher from baseline to post ingestion for the placebo condition ($p<.001$, $g=0.93$), with no differences for the modafinil condition. Vigour-activity was significantly lower from baseline to post-ingestion in the placebo condition ($p<.001$, $g=1.07$), with no differences in the modafinil condition. There was no significant Time x Drug x Sex interactions for any of the POMS subscales.

There was a significant Time x Drug interaction for the KSS. Planned comparisons revealed a significant increase in fatigue from baseline to post-ingestion for the placebo condition ($p=.004$, $g=0.65$). The Time x Drug x Sex interaction for the KSS was not significant.

Table 3

Means for Mood (POMS), Fatigue (KSS) and Subjective Performance (VAS) Measures

Measures	Modafinil		Placebo	
	Baseline	Post Ingestion	Baseline	Post Ingestion
POMS measures:				
Total score	12.2 (9.1)	13.0 (8.3)	12.4 (10.3)	13.2 (11.7)
Tension-Anxiety	1.73 (2.9)	1.49 (2.3)	1.68 (3.4)	1.24 (2.2)
Depression-Dejection	0.84 (1.9)	0.51 (1.1)	0.03 (0.2)	1.05 (2.9)
Anger-Hostility	0.16 (0.9)	0.08 (0.3)	0.11 (0.4)	0.43 (1.2)
Vigour-Activity	6.49 (5.0)	7.43 (4.5)	7.00 (5.9)	3.76 (3.1)
Fatigue-Inertia	2.38 (2.4)	2.16 (2.3)	2.60 (3.1)	5.11 (4.5)
Confusion-Bewilderment	1.22 (1.7)	1.32 (2.4)	0.97 (2.2)	1.60 (2.7)
KSS	4.47 (1.5)	4.39 (1.4)	3.92 (1.8)	5.39 (1.9)
VAS Performance measures:				
Alert	32.4(13.5)	9.5 (17.93)	21.1 (12.2)	6.75 (14.1)
Task Ability	24.5 (20.4)	18.9 (22.3)	21.1 (19.8)	17.3 (23.4)
Impaired Driving	34.5 (17.3)	10.8 (17.6)	21.8 (14.1)	8.67 (18.1)
Drive Safely	45.3 (23.3)	30.3 (29.0)	42.1 (24.4)	24.1 (26.9)

Table 4

Main Effects and Interactions for Mood and Fatigue Measures

	Time			Drug			Time x Drug			Time x Drug x Sex		
Measures	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2
POMS subscales:												
Total Mood	0.26	.603	.008	0.01	.906	<.001	0.16	.696	.004	2.33	.136	0.06
Disturbance												
Tension-Anxiety	1.61	.213	.043	0.19	.670	.005	0.12	.736	.003	0.41	.710	0.004
Depression-Dejection	1.82	.186	.048	0.54	.469	.015	6.60	.014	.155	2.65	.315	0.03
Anger-Hostility	1.34	.255	.036	1.60	.214	.042	1.73	.197	.046	0.04	.850	0.001
Vigour-Activity	3.69	.063	.093	7.07	.012	.164	18.59	p<.001	.340	0.04	.949	<.001
Fatigue-Inertia	4.92	.033	.120	11.63	.002	.245	11.88	.001	.248	5.54	.336	0.03
Confusion-	2.92	.096	.075	0.003	.958	<.001	1.53	.224	.041	2.42	.222	0.04
Bewilderment												
KSS	7.68	.009	.180	0.59	.446	.017	16.67	p<.001	.323	0.87	.356	0.03

Subjective Performance and Drug Effects

There was a significant main effect of Time for the statement relating to the perceived ability to drive safely (Table 5). Participants perceived ability to drive safely was higher at baseline than post-ingestion. There was a significant main effect of Drug for the statements relating to perceived task ability and perceived ability to drive safely. Participants perceived task ability was higher in the modafinil condition compared to placebo. Participants perceived ability to drive safely was also higher in the modafinil condition placebo. There was a significant Time x Drug interaction for the statements relating to alert level and perceived driving impairment. Planned comparisons indicate a significant increase in alertness from baseline to post-ingestion after modafinil ($p=.013$, $g=0.49$) and a significant decrease in alertness from baseline to post ingestion after placebo ($p=.007$, $g=0.62$). There were significant increases in both modafinil ($p=.004$, $g=0.47$) and placebo conditions ($p<.001$, $g=0.89$) from baseline to post ingestion in perceived driving impairment. The Time x Drug x Sex interaction was not significant for any of the VAS statements.

For VAS of subjective drug effects at post-ingestion, participants reported significantly stronger drug effects in the modafinil condition ($M=37.97$, $SD=30.32$) than the placebo condition ($M=23.03$, $SD=22.81$), $t(36)=2.57$, $p=0.15$, $g=0.55$). The liking of the drug effect was stronger in the modafinil condition ($M=57.62$, $SD=21.53$) than placebo ($M=44.70$, $SD=15.95$), $t(36)=3.12$, $p=.004$, $g=0.67$. Participants were more alert in the modafinil condition ($M=63.51$, $SD=25.90$) than the placebo condition ($M=43.84$, $SD=23.09$), $t(36)=3.85$, $p<.001$, $g=0.79$. There was no difference between modafinil ($M=9.47$, $SD=15.56$) and placebo conditions ($M=9.08$, $SD=16.96$) in the perceived intoxication level, $t(36)=0.12$, $p=.907$, $g=0.02$. The Drug x Sex interaction was not significant for any of the VAS drug effects statements.

Table 5

Main Effects and Interaction Results for VAS Subjective Performance Measures

Measures	Time			Drug			Time x Drug			Time x Drug x Sex		
	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2
Alert	55.87	p<.001	.615	17.81	p<.001	.337	8.20	.007	.190	0.15	.697	0.005
Task Ability	1.26	.270	.035	6.20	.018	.150	0.63	.432	.018	0.17	.684	0.005
Impaired Driving	45.07	p<.001	.563	22.25	p<.001	.389	9.04	.005	.205	0.45	.507	0.01
Drive Safely	24.74	p<.001	.414	11.61	.002	.249	0.63	.434	.018	2.61	.115	0.07

Reaction Time

A repeated measures ANOVA revealed a significant main effect of Cue (Table 6). Pairwise comparisons revealed that reaction time was significantly faster following central cue trials ($M=510$, $SD=51$) than no cue trials ($M=529$, $SD=53$). Reaction time was also significantly faster following spatial cue trials ($M=461$, $SD=48$) than central cue trials. The reaction time following spatial cue trials was significantly faster than trials following no cue. There was a significant main effect of Sex. The reaction time for males ($M=475$, $SD=49$) was significantly faster than the reaction time for females ($M=525$, $SD=49$).

The Time x Drug interaction was significant. Pairwise comparisons were conducted for each drug condition on each time point. Reaction time for the modafinil condition was faster at post-ingestion than baseline but this did not reach significance but did produce a small effect, ($p=.081$, $g=0.25$). The reaction time for the placebo condition did not differ between baseline and post-ingestion.

The Time x Cue interaction was significant. Pairwise comparisons were conducted separately for each cue type. Reaction time for spatial cues was significantly faster at post-ingestion than at baseline ($p=.042$, $g=0.21$). There were no significant differences between baseline and post-ingestion for central cue ($p=.277$, $g=0.13$) or no cue types ($p=.784$, $g=0.03$).

The Time x Drug x Cue interaction was not significant, but hypothesis driven pairwise comparisons were conducted for Time for each cue type and drug condition (See Figure 2). There was a small significant decrease in reaction time for central cue trials in the modafinil condition from baseline to post-ingestion ($p=.038$, $g=0.30$) and a small non-significant increase in reaction time between baseline and post-ingestion for the placebo condition ($p=.249$, $g=0.11$). For targets following no cue, there was a small non-significant

decrease in reaction time between baseline and post-ingestion for the modafinil condition ($p=.365$, $g=0.15$) and a small increase in reaction time between baseline and post-ingestion for the placebo condition ($p=.010$, $g=-0.25$). For spatial cue trials, there was a small significant decrease in reaction time from baseline to post-ingestion for modafinil ($p=.017$, $g=0.31$) and a negligible non-significant difference between baseline and post ingestion for placebo ($p=.648$, $g=0.04$).

The hypothesised Sex x Cue interaction was not significant. Hypothesis driven pairwise comparisons were conducted separately for each cue type. For no cue trials, males had a large significantly faster reaction time than females ($p=.013$, $g=0.87$). For central cues, males had a large significantly faster reaction time when compared to females ($p=.010$, $g=0.91$). For spatial cues, males had a large significantly faster reaction time than females ($p=.002$, $g=1.15$).

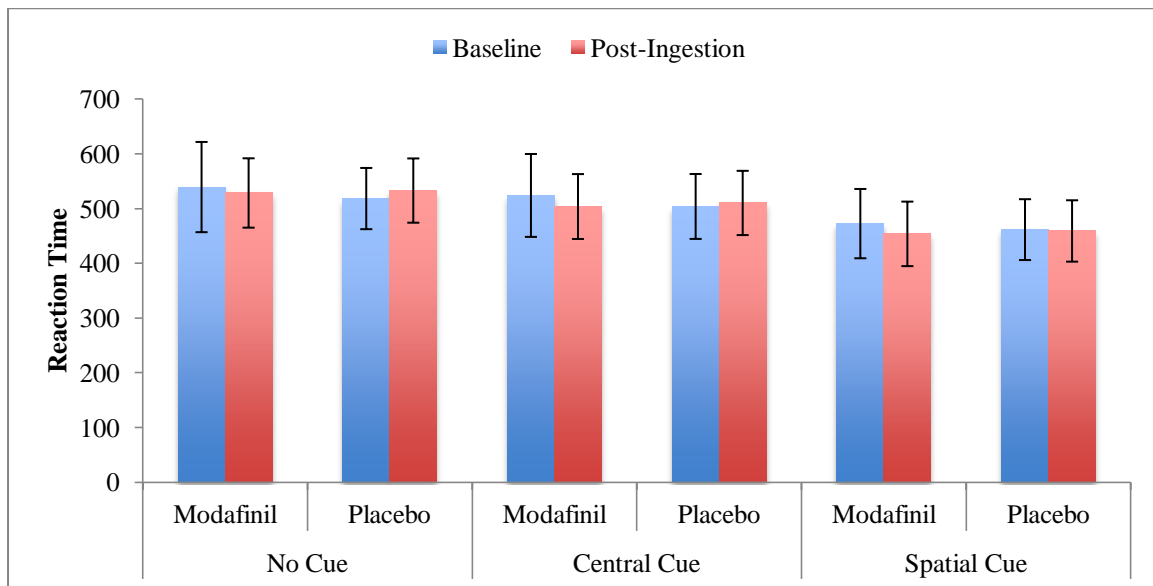


Figure 2. Reaction Time at Baseline and Post Ingestion for Drug Condition and Cue Type (error bars represent 95%CI's).

Table 6

Main Effects and Interaction Results for Reaction Time Analyses

Factor	<i>F</i>	<i>df</i>	<i>p</i>	η_p^2
Time	0.78	1, 34	.384	.022
Drug	0.46	1, 34	.502	.013
Cue	343.59	1.6 53.8	<.001	.910
Sex	8.74	1, 34	.006	.204
Time x Sex	0.08	1, 34	.774	.002
Drug x Sex	1.80	1, 34	.189	.050
Cue x Sex	1.64	1.6, 53.8	.207	.046
Time x Drug	5.94	1, 34	.020	.149
Time x Cue	10.04	1.9, 64.3	<.001	.228
Drug x Cue	1.54	1.9, 64.6	.221	.043
Time x Cue x Sex	1.37	1.9, 64.3	.262	.039
Time x Drug x Sex	0.009	1, 34	.924	<.001
Drug x Cue x Sex	0.60	1.9, 64.6	.554	.017
Time x Drug x Cue	1.67	1.7, 56.5	.202	.047
Time x Drug x Cue x Sex	0.23	1.7, 56.5	.754	.007

Accuracy

A repeated measures ANOVA revealed a significant main effect of Time (Table 7). Accuracy was significantly higher at baseline ($M=95.71$, $SD=3.30$) than post-ingestion ($M=93.94$,

$SD=4.05$). There was also a significant main effect of Drug. Accuracy was significantly higher after modafinil ingestion ($M=95.39$, $SD=3.37$) than after placebo ($M=94.27$, $SD=3.80$). The main effect of Cue was significant. Accuracy was significantly higher following spatial cues ($M=95.74$, $SD=3.34$) than following both no cue ($M=94.85$, $SD=3.56$) and central cue trials ($M=93.90$, $SD=3.62$). Accuracy following no cue was significantly higher than following central cues. There were no significant effects related to Sex.

Table 7

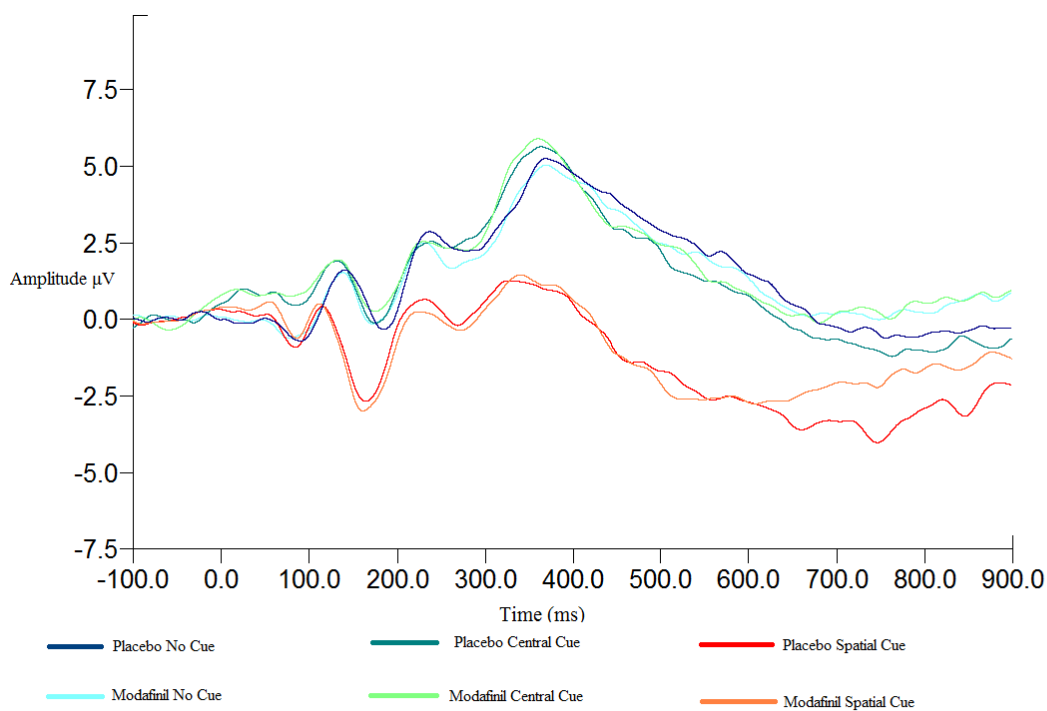
Main Effects and Interactions Results for Accuracy Analyses

Factor	F	df	p	η_p^2
Time	10.21	1,34	.003	.231
Drug	5.57	1, 34	.024	.141
Cue	14.32	1.9, 66.2	<.001	.298
Sex	0.90	1, 34	.351	.026
Time x Sex	0.61	1, 34	.442	.017
Drug x Sex	0.31	1, 34	.582	.009
Cue x Sex	1.26	1.9, 66.2	.290	.036
Time x Drug	2.21	1, 34	.146	.061
Time x Cue	2.48	1.7, 58.4	.100	.068
Drug x Cue	0.61	1.7, 56.5	.516	.018
Time x Cue x Sex	1.12	1.7, 58.4	.332	.032
Time x Drug x Sex	0.66	1, 34	.424	.019
Drug x Cue x Sex	0.56	1.7, 56.5	.543	.016

Time x Drug x Cue	2.19	1.9, 66.1	.122	.060
Time x Drug x Cue x Sex	0.19	1.9, 66.1	.823	.006

N1 Amplitude

A repeated measures ANOVA revealed a significant main effect of Cue for N1 amplitude at post-ingestion (Table 8, Figures 3 & 4). Pairwise comparisons revealed that N1



amplitude was significantly greater following central cue trials ($M=-2.06$, $SD=2.93$) than following no cue trials ($M=-1.35$, $SD=2.42$). N1 amplitude was also significantly greater following spatial cue trials ($M=-4.53$, $SD=2.68$) than following both central cue and no cue trials.

Figure 3. Grand Mean Waveforms for Each Cue Type by Drug Condition for Females at Occipital Site OZ

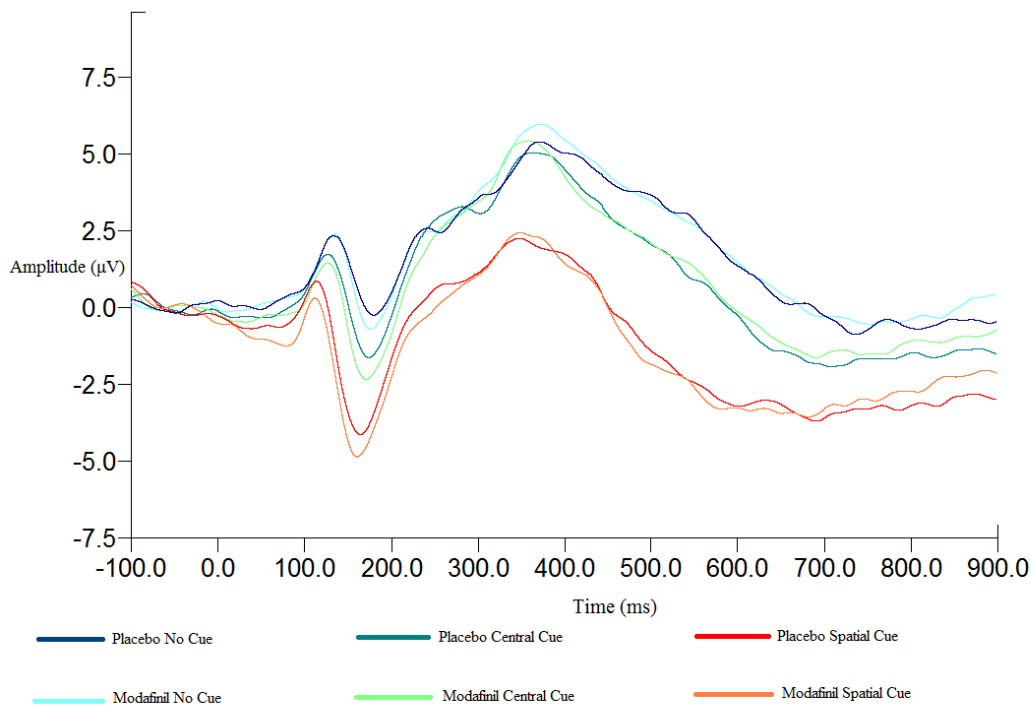


Figure 4. Grand Mean Waveforms for Each Cue Type by Drug Condition for Males at Occipital Site OZ

The main effects of Drug and Sex were both non-significant, but there was a significant Drug x Sex interaction. Pairwise comparisons were conducted comparing modafinil and placebo conditions for each sex. For females, the effect of drug was not significant ($p=.206$, $g=0.15$). For males, the effect of drug was significant, with N1 amplitude significantly greater in the modafinil condition than the placebo condition ($p=.039$, $g=0.24$).

The hypothesised Drug x Cue interaction was not significant. Planned hypothesis driven comparisons were conducted on drug condition separately for each cue type. There was no significant difference between modafinil and placebo conditions for any of the cue type, no cue ($p=.263$, $g=0.08$), central cue ($p=.985$, $g<.001$) or spatial cue ($p=.683$, $g=0.06$).

Table 8

Main Effects and Interactions Results for N1 Amplitude at post-ingestion

Factor	<i>F</i>	<i>df</i>	<i>p</i>	η_p^2
Drug	2.20	1, 34	.147	.061
Cue	54.35	1.5, 50.4	<.001	.615
Sex	1.60	1, 34	.215	.045
Drug x Sex	5.64	1, 34	.023	.142
Cue x Sex	2.15	1.5, 50.4	.139	.060
Drug x Cue	0.41	1.6, 54.3	.619	.012
Drug x Cue x Sex	2.25	1.6, 54.3	.126	.062

Discussion

The aim of the present study was to investigate the effect of 200mg of modafinil on attentional alerting and orienting networks in a healthy non-sleep deprived sample using an attentional network task. A further aim was to examine both male and female participants to investigate any associated sex differences in attention and modafinil effects. As hypothesised and consistent with Neuhaus et al. (2010), reaction time decreased as cues became more informative. Reaction time was significantly faster for central cues than no cue trials, and significantly faster for spatial cues when compared to both central and no cue trials. This pattern was also found for N1 amplitude, supporting the hypothesis and the findings of Neuhaus et al. (2010), that N1 amplitude would increase as cues became more informative. Consistent with the hypothesis, there was a small enhancement of the alerting network, demonstrated by a small decrease in reaction time from baseline to post-ingestion for

modafinil but not placebo. There also appeared to be a small enhancement of the orienting network which was not hypothesised, as reaction time for spatial cues was faster at post-ingestion than at baseline, but this effect was not greater than the alerting effect. Reaction time for males was faster overall for males and males also showed faster reaction time for each cue type, which was not hypothesised. Males showed a greater N1 amplitude after modafinil than placebo which was not present for female participants, indicating that modafinil may effect the sexes differently.

Mood, Fatigue and Alertness

There was a significant increase in fatigue (KSS) and fatigue-inertia (POMS) from baseline to post-ingestion for the placebo condition but not modafinil. Vigour-activity significantly decreased from baseline to post-ingestion in the placebo condition. Alertness (VAS) was significantly higher from baseline to post-ingestion for modafinil and lower for placebo. Perceived driving ability and perceived task ability were both higher in the modafinil condition than the placebo condition. These results suggest that overall; modafinil decreases fatigue and increases overall alertness, which is supported by other studies (Baranski et al. 2004; Ikeda et al. 2017).

The depression-dejection subscale decreased significantly from baseline to post-ingestion in the modafinil condition but not placebo. This is consistent with modafinil inhibiting the reuptake of dopamine, creating feelings of euphoria, and suggests why modafinil is becoming more commonly used in treatment of depression (Minzenberg & Carter, 2008).

Attentional Network Task

There was a significant decrease in reaction time between no cue and central cue trials as hypothesised. There was also a significant decrease in reaction time between central cue and spatial cue trials, which was also hypothesised. These findings are consistent with Neuhaus et al. (2010), who found that reaction time decreases as the cue becomes more informative. Faster reaction time for central cues relative to no cue indicates activation of the alerting network, while faster reaction time for spatial cues relative to central cues indicates activation of the orienting network. This indicates activation of both alerting and orienting networks by their respective cue types in the attentional network task used in this study.

N1 amplitude was significantly greater (more negative) for central cues than no cue. N1 amplitude was also significantly greater for spatial cues than central cues. These results are consistent with the hypotheses, and also with Neuhaus (2010)'s findings. Neuhaus et al. (2010) found that N1 amplitude becomes greater as cues are more informative, indicating activation of both alerting (central cue) and orienting networks (spatial cue).

Alerting Network

The Time x Drug x Cue interaction for reaction time was not significant, however pairwise comparisons revealed some potential enhancement of the alerting network. The decrease in reaction time between baseline and post-ingestion was small and significant for the modafinil condition, but was not significant for the placebo condition. This suggests some alerting network enhancement after modafinil ingestion. This is consistent with the hypotheses that modafinil would enhance the alerting network and consistent with some previous research. Studies that have used a more complex task have found consistent effects of modafinil on the alerting network (Baranski et al. 2004; Cope et al. 2017; Ikeda et al.

2017; Theunissen et al. 2009). Ikeda et al. (2017) found that in an attentional network task, participants had a faster reaction time after modafinil compared to placebo. Using a Mackworth clock test, faster reaction time was also found after modafinil ingestion when compared to placebo (Theunissen et al. (2009). Modafinil also improved accuracy on the attentional network task in this study, consistent with Cope et al. (2017) and Baranski et al. (2004) who found that modafinil ingestion resulted in increased ability to detect targets on a 5-choice continuous performance task and a detection of repeated numbers task respectively.

These results are not consistent with some previous research that has found no effect of modafinil on the alerting network. These tasks are simple in nature and have been suggested to not be complex enough to detect differences between modafinil and placebo conditions in a healthy population due to ceiling effects (Battleday & Brem, 2015). Turner et al. (2003) and Randall et al. (2005) used a RVIP task to analyse sustained attention and both found that modafinil did not improve performance on the task. A reaction time task also failed to find any enhancing effects of modafinil on the alerting network (Liepert et al. (2004). The results of the current study are not consistent with these findings, with some enhancement of the alerting network found.

The Drug x Cue interaction and associated planned comparisons, specifically for central cues were not significant. This suggests no enhancement of the alerting network for this dependent variable following modafinil ingestion. The result is inconsistent with the reaction time results, which showed some alerting network enhancement on further investigation of the results. As this is the first study to use N1 amplitude as a dependent variable, there are no comparisons studies to help explain why these results have occurred.

Orienting Network

While the Time x Drug x Cue interaction was not significant, pairwise comparisons revealed that there was a small decrease in reaction time from baseline to post-ingestion for modafinil that was not present for placebo. It was hypothesised there would be no difference between modafinil and placebo conditions following spatial cues, consistent with Ikeda et al. (2017). The effect found was small and was similar in size to the effect found for the alerting network. As spatial cues also include an alerting component (warns participants to oncoming target as well as location), it is possible that the effect found is related to enhancement of the alerting network rather than specific enhancement of the orienting network (Petersen & Posner, 2012).

Consistent with the hypothesis, there was no difference between modafinil and placebo conditions in N1 amplitude for spatial cues. This result suggests that there was no enhancement of the orienting network after modafinil ingestion, which is consistent with Ikeda et al. (2017). As little research has been conducted into the effect of modafinil on the orienting network, more is needed to determine possible effects.

Sex Differences in Attentional Networks

It was expected that female participants would have a faster reaction time to spatial cues than male participants. However, the results showed that male participants had a faster reaction time overall and also for each specific cue type. Merritt et al. (2007) found that males had a faster overall reaction time on a spatial cuing task, which is consistent with the findings of this study. However, it was not expected that males would respond to spatial cues faster than female participants, as Merritt et al. (2007) also found that females showed a benefit to valid cues (present in the ANT) and males showed a benefit to invalid cues (not

present in the ANT). Liu et al. (2013) found that females responded to spatial cues faster in an attentional network task than males, and found no difference between the sexes for central and no cue types. This is the first study to find a difference between males and females on central and no cue types (Liu et al. 2013; Xiao et al. 2016). There were more male participants recruited than females, which could indicate why this effect occurred due to the lack of power in the female sample.

There was no difference between females and males in N1 amplitude for any cue type. This is inconsistent with findings by Neuhaus et al. (2009) who found females had greater N1 amplitude after spatial cues than males. Males showed greater N1 amplitude following modafinil compared to placebo than females. This is the first study to investigate the differential effects of modafinil on males and females. Therefore, these results could indicate that modafinil could have a greater impact on males than females, but more research would be required to confirm this, as in the current study the female sample lacked power to detect any true differences.

Implications

This is the first study to investigate the effects of modafinil on ERP measures of attention (N1 component) and also include both male and female participants. The results suggest some small alerting network enhancement and potentially orienting network enhancement. While small in nature, these effects suggest that modafinil can be effective to enhance some aspects of attention (mainly alerting network). As modafinil is commonly used by shift workers, it is likely to result in some improvement in attention when compared to no drug (Minzenburg & Carter, 2008). Males showed greater N1 amplitude after modafinil than females, suggesting some sex differences in the effects of modafinil. However, more research

is needed to confirm this finding. This study only investigated the effects of modafinil on attention based on a single dose of modafinil. Future studies should investigate the effect of repeated doses of modafinil to determine if the enhancing effects are likely to be effective for long-term use. Modafinil could also be investigated in comparison to other possible attention enhancers such as caffeine to determine if modafinil is the best choice as a cognitive enhancer (Brunyé, Mahoney, Lieberman, & Taylor, 2010).

Limitations

The sample size for the current study was inconsistent across the sexes, with more male participants recruited than female participants. This is an issue for the power of the statistical analyses involving sex as a factor. This is because the female sample was small, and therefore lacked sufficient power to detect any differences (Button et al. 2013). For future studies, it would be ideal to have equal samples of each sex to more accurately determine the sex differences in attention and if modafinil has differential effects.

The findings into the effects of modafinil on the attentional networks has been mixed. A possible reason is because the tasks used are not complex enough to detect the effects of modafinil in a healthy non-sleep deprived sample with an overall high IQ. The sample for the present study primarily included university students (79.9%), with a mean WTAR score higher than average. The general high IQ of this sample could indicate that the task was not complex enough to detect the effects of modafinil in this sample, as many hypothesised interactions were non-significant. Future studies should attempt to use a more diverse sample or incorporate IQ into the analysis (Randall et al. 2005) to more accurately determine the effects of modafinil on attention.

Baseline ERP measure were not collected in the present study for comparison to the post-ingestion data. The time constraints for the present study meant that it was not feasible to collect ERP data at both baseline and post-ingestion due to the time consuming nature of the EEG set-up. Future studies should incorporate baseline ERP measures for comparison to post-ingestion if time is not an issue.

Another potential limitation is that peak plasma levels were only estimated based on other modafinil research rather than using blood samples from each participant. This means that the time of testing may not have been ideal for each participant due to individual differences in rates of absorption. While invasive due to the need to collect blood samples, future studies should base time of testing on each individual participant rather than estimating based on other research.

As participants were more likely to think that they had taken modafinil in the modafinil condition, it is possible that some expectancy effects occurred. Participant's expectations about how they should be reacting after the drug ingestion could have affected their overall results to support those expectancies. A double-blind procedure was used to try and eliminate these effects. Furthermore, as participants were generally only on average around 50% sure they had taken modafinil, these effects would have likely been minimal.

Conclusion

The aim of the current study was to investigate the effects of 200mg of modafinil on behavioural (reaction time) and neural (N1 amplitude) measures of attentional alerting and orienting networks in a healthy non-sleep deprived sample. Reaction time and N1 amplitude decreased and increased respectively as cues became more informative, indicating activation of the respective networks (Neuhaus et al., 2010). Pairwise comparisons indicate a small

significant enhancement of the alerting network, demonstrated by a decrease in reaction time from baseline to post-ingestion for modafinil but not placebo. This was consistent with the hypotheses relating to the alerting network. However, N1 amplitude was not greater after modafinil ingestion as expected, and conflicting with the reaction time results. Future research is needed to investigate these effects further.

There was a small significant decrease in reaction time from baseline to post-ingestion for spatial cues. This effect similar to the alerting effect, and was likely due to the alerting enhancement rather than specific enhancement of the orienting network. There was no increase in N1 amplitude after modafinil, as expected.

The hypotheses relating to sex differences were all not supported, with males revealing faster reaction time overall and for each specific cue type. This is the first study to suggest a difference between males and females for both central cues (alerting) and no cue types. There was no difference between males and females for N1 amplitude, which was not expected. A reason for these findings could relate to the sample size, with more male participants recruited than female participants. Males showed greater N1 amplitude after modafinil ingestion when compared to placebo than females did. No other study has looked at sex differences in the effects of modafinil and this needs to be further investigated.

These findings are consistent with previous findings into alerting enhancement after modafinil. However, the orienting network has not been substantially researched and more research is required to determine if modafinil does have some enhancing effects on this network. While executive control was not the focus of the current study, future study should also investigate the effects of modafinil on this network, particularly ERP measures. Future studies should also aim to investigate the effects of modafinil on both sexes, with equal

sample sizes. Other limitations should also attempt to be addressed, including recoding baseline ERP data and accurately determining peak plasma levels of modafinil in participants.

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Appendix D: Modafinil Consumer Medical Information

Appendix E: Screening Questionnaire

Appendix F: Experimental Questionnaire

Appendix A: Ethics Approval

From: human.ethics@utas.edu.au [<mailto:human.ethics@utas.edu.au>]
 Sent: Thursday, 27 July 2017 11:03 AM
 To: Raimondo Bruno <raimondo.bruno@utas.edu.au>
 Cc: chris.wake@ths.tas.gov.au; Allison Matthews <allison.matthews@utas.edu.au>; Jessica Hartley <jessica.hartley@utas.edu.au>; Research Ethics <Human.Ethics@utas.edu.au>
 Subject: Notification of Amendment Approval: H0011386 The effect of modafinil on simulated driving performance

Dear AssocProf Bruno,
 Ethics Ref: H0011386
 Title: The effect of modafinil on simulated driving performance

This email is to confirm that the following amendment was approved by the Chair of the Tasmania Health and Medical Human Research Ethics Committee on 27/7/2017:
 Amendment to assist with recruitment and to allow investigation of sex differences in cognitive processing, the recruitment criteria will be broadened to include females

Miscellaneous Modafinil_poster_revised_2017 Information Sheet MODAFINIL info and consent forms_revised_2017 Miscellaneous MODAFINIL_questionnaires_revised2017 Application Form revised NEAF - Modafinil_NEAF_amendment_210717

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the National Statement on Ethical Conduct in Human Research (NHMRC 2007).

This email constitutes official approval. If your circumstances require a formal letter of amendment approval, please let us know.

Should you have any queries please do not hesitate to contact me.

Kind regards
 Christy Nixon

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Appendix B: Information Sheet

INFORMATION SHEET



The Effect of Modafinil on Cognitive Processes and Brain Activity

Chief Investigators: Dr Raimondo Bruno & Dr Allison Matthews

Researchers: Tanya Wilson and Hannah Shaw *

**This research is being conducted as part of an Honours degree in the School of Psychology, UTAS.*

We would like to invite you to participate in a study aiming to better understand the way that the prescription drug Modafinil effects cognitive processes such as attention and associated brain activity. The use of this drug is increasing Australia wide, and we are interested in better understanding its effects. There have been a number of studies which have shown some effects of stimulant drugs on cognitive processes but very few studies have examined Modafinil. Getting a better understanding about Modafinil is particularly important, not just to understand how the drug affects cognition, but also to be able to provide information for doctors to give to potential users of the drug.

Why have I been invited to participate in this research?

You are invited to take part in the study if you are aged 18-30 years old. In order for the results of the study to be clear, all participants need to speak English fluently, and have had no previous neurological or mental health problems. In addition participants must NOT use illicit drugs, smoke cigarettes daily, consume alcohol at harmful levels. All females will need to indicate that there is no chance that they might be pregnant, and are recommended to refrain from sexual intercourse for 48 hours after each experimental session to reduce any potential of harm if a pregnancy was to arise. In addition, females currently on hormonal contraception (e.g., the contraceptive pill and implanon) will need to be willing to abstain from sex or use barrier-based contraception (e.g., condoms) during and for four weeks after the study. This is based on evidence that Modafinil may decrease the effectiveness of hormone-based contraceptives. This advice does not apply to the following forms of contraception which should remain effective: depo-provera injections, mirena or copper IUDs.

What will my participation involve?

Participating in this study is unlikely to cause any discomfort or distress. Firstly, if you are interested in taking part in the study, you will be invited to complete a series of confidential screening questionnaires. These will enquire about what your mood has been like recently. This will include a psychological distress scale, schizotypal personality questionnaire, a psychosis screener and some questions regarding your alcohol and drug use. All data collected will be kept in the strictest confidence, and the way we maintain this is described below. This screening process is simply to ensure that participants in the study are not taking medications or experiencing other issues that may cause a negative response to Modafinil.

During the study, we will ask for some basic information about yourself (such as age, sex, years of schooling). During each testing session, you will be fitted with an electrode cap for measuring your brain activity. You will be asked to complete some computer-based tasks which relate to cognitive processes such as attention. In these tasks you will respond with a button press when particular stimuli appear on the screen. Previous studies using the same dose of Modafinil have found side effects for some participants, including dry mouth, mild headaches and mild nausea. There will be two testing sessions which will occur at the University of Tasmania, and will take around four hours each. You will be reimbursed \$80 for your time and out-of-pocket expenses.

Before taking part in the study you must organise for a reliable friend or family member to collect you from the lab at the end of the testing session, in case you are still experiencing any effects following the possible administration of Modafinil. The researcher will check that this has been organised before the testing session begins. When the nominated person collects you, they will be given a copy of the medication information sheet about Modafinil, and the main points will be verbally explained. Namely, it will be explained that they should ensure you do not drive a vehicle or operate machinery for the rest of the day, and do not consume alcohol. In the unlikely event that you do experience unpleasant side effects while completing the testing, the researchers are trained in first aid, and the chief investigators will be available on site to provide further assistance if required. Additionally, the researcher will explain that in the unlikely event of you experiencing an adverse reaction once you have left the premises, you should contact your doctor or be taken to hospital immediately.

There are no specific risks associated with the measurement of brain activity. However, if you have sensitive skin there is a small possibility of a slight skin reaction from electrode preparation materials. If you believe there is a chance that your skin may react you are advised to reconsider participation.

How private is the information that I give?

It is important for you to know that all data collected will be kept in the strictest confidence. All data will be identified by a coding system and no names or contact numbers will appear on any records. In this way, your identity is protected, and there will be no risk of legal or social problems arising from your participating in the study. All information gathered in the study will be reported as grouped data, and because no personal information is recorded, no individual participants will be identifiable in the research output. Data from the study will be stored securely for five years in locked cabinets in the School of Psychology, as is legally required, and then destroyed by shredding.

Can I withdraw from the research if I wish?

Participation in this study is entirely voluntary. You may, at any time, decline to answer any question you so wish, or withdraw from the study without effect or explanation. You will be given a copy of this information sheet to keep. Please retain this information

sheet in case you decide at a later date that you would like to retract your data from the study.

Who do I need to contact if I have any questions about the research?

If you would like more information about the research, please contact Dr Allison Matthews on 6226 7236 (or email Allison.Matthews@utas.edu.au) or Dr Raimondo Bruno 6226 2190 (Raimondo.Bruno@utas.edu.au). If you would like to find out about the results of the study, these will be available from Dr Matthews after November 2016 or at www.utas.edu.au/psychol.

Has this research been approved by an ethics committee?

This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. Please quote the ethics reference number H11386.

Who can I contact if I have any concerns?

If you have any personal concerns related to the study, you may choose to discuss these concerns confidentially with a counsellor at the University Psychology Clinic free of charge. Confidential appointments may be made on (03) 6226 2805.

Thank you for your interest in the study and for taking the time to read this information sheet. We hope you will be interested in participating in this study.

Raimondo Bruno & Allison Matthews
Chief Investigators
(03) 6226 2190 or (03) 6226 7236

Tanya Wilson/Hannah Shaw
Student Researchers

Appendix C: Consent Form

CONSENT FORM

The Effect of Modafinil on Cognitive Processes and Brain Activity

1. I have read and understood the 'Information Sheet' for this study.
2. I have read and understood the 'Consumer Medicine Information' regarding modafinil.
3. The nature and possible effects of the study have been explained to me. I understand that I should refrain from sex for 48 hours after each experimental session to reduce potential harm if an unplanned pregnancy were to arise. I may also need to abstain from sex or use barrier-based contraception (e.g., condoms) during and for four weeks after the study to ensure effectiveness of certain forms of hormonal contraception (e.g., the contraceptive pill and implanon).
4. I understand that the study involves:
 - Attending two testing sessions of approximately four hours duration
 - Completing a series of cognitive tasks while my brain activity is measured
5. I understand that all research data will be securely stored on the University of Tasmania premises for five years, and will then be destroyed.
6. Any questions that I have asked have been answered to my satisfaction.
7. I agree that research data gathered from me for the study may be published provided that I cannot be identified as a participant.
8. I understand that the researchers will maintain my identity confidential and that any information I supply to the researcher(s) will be used only for the purposes of the research.
9. I agree to participate in this investigation and understand that I may withdraw at any time without any effect, and if I so wish, may request that any data I have supplied to date be withdrawn from the research.
10. This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. Please quote the ethics reference number H11386.

Name of Participant:

Signature:

Date:

Statement by Investigator

☐ I have explained the project & the implications of participation in it to this volunteer (including the potential for modafinil to reduce the effectiveness of hormonal contraception) and I believe that the consent is informed and that he/she understands the implications of participation

Name of Investigator

Signature:

Date:

Appendix D: Modafinil Consumer Medical Information

MODAVIGIL®

Modafinil

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about MODAVIGIL® tablets. As this leaflet does not contain all the available information, it is important that you talk to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you receiving MODAVIGIL® against the benefits this medicine is expected to have for you.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet. You may need to read it again.

What MODAVIGIL® is used for

MODAVIGIL® is used to improve wakefulness in people with excessive daytime sleepiness associated with the medical condition known as narcolepsy or with Obstructive Sleep Apnoea/Hypopnoea Syndrome (OSAHS), or shift work sleep disorder (SWSD).

In narcolepsy, there is a sudden and irresistible tendency to fall asleep during normal waking hours. This happens at unpredictable times, even when it is inappropriate or may be unsafe to do so. MODAVIGIL® decreases this unwanted excessive daytime sleepiness.

With OSAHS, daytime sleepiness may occur due to an interrupted night time sleep. MODAVIGIL® only treats the symptom of sleepiness and does not treat the cause of OSAHS. Whilst taking MODAVIGIL® you should continue with treatments intended to help manage your underlying medical condition, such as Continuous Positive Airway Pressure, unless your doctor tells you otherwise.

MODAVIGIL® may also help to keep you awake during your working shift if you have been diagnosed with moderate to severe chronic Shift Work Sleep Disorder (SWSD).

Precisely how MODAVIGIL® works is not known, but it is known that it acts on the central nervous system (the brain). It differs from other stimulant medicines that promote wakefulness. MODAVIGIL® increases wakefulness. Unlike other stimulants it does not overstimulate or produce a "high" feeling.

Your doctor may have prescribed MODAVIGIL® for another reason. Ask your doctor if you have any questions about why MODAVIGIL® has been prescribed for you.

Before you take MODAVIGIL®

When you must not take it

You must not take MODAVIGIL® if you:

- are allergic to modafinil or any of the other ingredients listed at the end of this leaflet. (See "MODAVIGIL® tablets description"). Signs of allergic reaction may include a skin rash, itching, shortness of breath or swelling of the face, lips or tongue
- are pregnant, or likely to become pregnant.

Do not take MODAVIGIL® if the packaging is torn or shows signs of tampering or the tablets do not look quite right.

Do not take MODAVIGIL® if the expiry date on the pack has passed.

If you are not sure about whether you should start taking MODAVIGIL®, you should contact your doctor.

Before you take it

Before you start taking MODAVIGIL® you should discuss with your doctor any of the following points which apply to you. If you:

- are under 18 or over 65 years old
- have a history of mental health problems
- have heart problems, including, for example, angina (chest pain), previous heart attack, enlarged heart
- have an abnormal/irregular heart rhythm
- have high blood pressure or your high blood pressure is controlled by medication

- have kidney or liver problems
- are taking hormonal contraceptives
- could become pregnant
- are currently receiving treatment for anxiety
- are breastfeeding
- are taking brain stimulants, such as methylphenidate
- are taking any medicines to treat depression, including those called monoamine oxidase inhibitors (MAOIs)
- are taking medicines to treat epilepsy or fits, such as phenytoin, carbamazepine and phenobarbitone
- are taking medicines to treat fungal infections, such as ketoconazole and itraconazole
- are taking medicines to help you sleep (sedatives)
- are taking rifampicin, an antibiotic used to treat tuberculosis
- are taking cyclosporin, a medicine used to stop organ transplant rejection
- are taking propranolol, a medicine used to treat, for example, high blood pressure, heart problems or migraine
- are taking warfarin, a medicine used to prevent unwanted blood clotting
- are taking theophylline, a medicine used in asthma and lung problems
- are taking any other medicines, including any available without a prescription from your pharmacy, supermarket or health food shop

Tell your doctor about any of the above before you take MODAVIGIL®. Your doctor will discuss the risks and benefits of using MODAVIGIL®.

How to take MODAVIGIL®

It is important that you take this medicine as directed by the doctor. Your doctor will tell you how much you should take, when and how often. Follow your doctor's instructions. If you are unsure ask your doctor or pharmacist.

How much should you take

Each MODAVIGIL® tablet contains 100mg of modafinil.

The usual daily dose of modafinil depends on individual response. For sleepiness associated with narcolepsy or OSAHS, the dose ranges from 200mg to 400mg.

Each day you should take either:

- two MODAVIGIL® tablets
- or
- up to four MODAVIGIL® tablets.

For SWSD, a dose of 200mg is recommended.

Do not exceed the recommended daily dose unless directed to do so by your doctor.

When and how should you take the tablets

For sleepiness associated with narcolepsy or OSAHS, you should take your MODAVIGIL® tablets either:

- as two separate doses, one in the morning and one at midday,
- or
- as one dose, in the morning.

For narcolepsy or OSAHS, do not take your MODAVIGIL® tablets later than midday, or you may have trouble sleeping at night.

For SWSD, you should take your MODAVIGIL® tablets as a single dose 1 hour prior to commencing your shift work.

Swallow the tablets whole with a little water.

NOTE: Your doctor may start your treatment with less than two tablets a day.

If you need more than two tablets per day, your doctor should increase the dose stepwise, one additional tablet at a time, depending on how you respond to the treatment. The highest dose is four tablets per day.

If you are currently on another treatment for narcolepsy, your doctor will advise you how best to withdraw from that treatment and begin taking MODAVIGIL®. Other stimulants used for narcolepsy may cause a "high" feeling. Be aware therefore that you may feel different as you withdraw from other stimulants. MODAVIGIL® is not associated with this "high" feeling. It works on excessive daytime sleepiness.

MODAVIGIL® only treats the symptom of sleepiness. Other treatments intended to help manage your underlying medical condition

should still be used regularly, unless your doctor tells you otherwise. You should commence or continue disease-modifying interventions (for example, Continuous Positive Airway Pressure).

REMEMBER: This medicine is only for you. Only a doctor can prescribe it for you. Never give it to anyone else. It may harm them, even if their symptoms appear to be the same as yours.

If you forget to take it

If you miss a dose of MODAVIGIL® tablets, just take the next dose at your usual time. Do not take an extra dose to "catch up".

While you are taking MODAVIGIL®

Things you must do

If you become pregnant while you are taking MODAVIGIL®, stop taking it and tell your doctor immediately.

If you are about to be started on any new medicine, tell your doctor and pharmacist that you are taking MODAVIGIL®.

Tell your doctor if you believe that MODAVIGIL® is not helping your condition. Your doctor may need to change the dose.

Things you must not do

Do not give MODAVIGIL® to anyone else, even if they have the same symptoms as you.

Things to be careful of

MODAVIGIL® may reduce the effectiveness of oral contraceptives. If you are using these forms of contraceptives while taking MODAVIGIL® (and for 1 month after you stop treatment with MODAVIGIL®) you should either use: an alternative birth control method or another effective birth control method together with your current contraceptive.

Do not drive or operate machinery until you know how MODAVIGIL® affects you.

Side Effects

MODAVIGIL® may cause you to have a serious rash.

Stop MODAVIGIL® and call your doctor right away or get emergency treatment if you have a skin rash, hives, sores in your mouth, or your skin blisters and peels, or if you have any sudden wheeziness, difficulty in breathing, swelling, rash or itching (especially affecting the whole body).

MODAVIGIL® may cause the following side effects in some people. In clinical studies, these side effects also occurred in people who received non-active (sugar) tablets. Tell your doctor if you notice any of these:

- headache
- nausea
- diarrhoea
- dry mouth
- poor appetite
- runny nose
- sore throat
- nervous feeling
- dizziness.

Tell your doctor immediately if any of the following occur:

- mental (psychiatric) symptoms. Symptoms include depression, anxiety, hallucinations, mania, thoughts of suicide or other mental problems.

Other side effects not listed above may also occur in some patients. Tell your doctor if you notice anything that makes you feel unwell. Do not be alarmed by this list of possible side effects. You may not experience any of them.

Overdosage

Immediately telephone your doctor, or the Poisons Information Centre (telephone 13 11 26 in Australia or 0800 764 766 in New Zealand), or go to the emergency department of your nearest hospital, if you think you or anyone else may have taken too much MODAVIGIL®. Do this, even if there are no signs of discomfort or poisoning.

MODAVIGIL® tablets description

Each MODAVIGIL® tablet contains 100mg of modafinil.

Each tablet also contains the following inactive ingredients:

- lactose
- starch-maize
- magnesium silicate dihydrate
- sodium croscarmellose
- povidone
- purified talc
- magnesium stearate.

MODAVIGIL® tablets are white, round-shaped with smooth convex sides.

Each pack contains either 10, 30 or 60 tablets.

Storage

Keep MODAVIGIL® tablets in the original pack until it is time to take them.

Store MODAVIGIL® tablets below 25 degrees C. Keep the pack in a cool, dry place and away from direct heat and sunlight.

Do not store MODAVIGIL® tablets in the bathroom or near a sink.

Keep MODAVIGIL® tablets where children cannot reach them. A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

The Australian Registration Number is AUST R 82350.

This is not all the information available on MODAVIGIL®. If you have any more questions or are unsure about anything, ask your doctor or pharmacist.

MODAVIGIL® is supplied in Australia by:

CSL Biotherapies
45 Poplar Road
Parkville 3052 VIC
AUSTRALIA

and in New Zealand by:

CSL Biotherapies (NZ) Limited
666 Great South Road
Central Park,
Auckland 6
NEW ZEALAND
Telephone: 09 579 8105

and manufactured by:

Cephalon France
20 rue Charles Martigny
94700 Maisons-Alfort
FRANCE

This leaflet was prepared in February 2009.

MODAVIGIL® is a registered trademark owned by Cephalon, Inc.

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Appendix E: Screening Questionnaire



Screening questionnaire

How old are you?

Participants must be males between 18 and 30.

Do you smoke?

If yes, participant is not eligible for the study.

Yes ☐ No ☐

Is English your first language?

Yes ☐ No ☐

For females: Are you currently pregnant or is there any chance that you could be pregnant or are you currently trying to conceive? (if Yes, exclude from the research)

Yes ☐ No ☐

For females: Are you currently using the following forms of hormonal contraception (contraceptive pill or implanon)?

Specify here _____

Yes ☐ No ☐

Note: the following advice does not apply to depo-provera injections, mirena or copper IUDs

If yes, would you be happy to abstain from sex or use barrier-based contraception for 4 weeks from the conclusion of the study?

Yes ☐ No ☐

Have you ever used any of the following:

Heroin

Yes ☐ No ☐

Methamphetamine (speed powder, base, ice)

Yes ☐ No ☐

Ecstasy

Yes ☐ No ☐

Cocaine

Yes ☐ No ☐

Hallucinogens (e.g. LSD, acid, magic mushrooms)

Yes ☐ No ☐

Inhalants (e.g. amyl nitrate, rush, glue, laughing gas, petrol, paint)

Yes ☐ No ☐

Other illicit drug

Yes ☐ No ☐

Have you ever used pharmaceutical medications without them being prescribed to you, e.g. morphine, methadone, oxycodone, pharmaceutical stimulants, antipsychotics, antidepressants?

Yes ☐ No ☐

Q1. How often do you have a drink containing alcohol?

0 Never	1 Monthly or less	2 2-4 times a month	3 2-3 times a week	4 4 or more times a week
----------------	--------------------------	----------------------------	---------------------------	---------------------------------

Q2. How many drinks containing alcohol do you have on a typical day when you are drinking?

0 1 or 2	1 3 or 4	2 5 or 6	3 7 to 9	4 10 or more
-----------------	-----------------	-----------------	-----------------	---------------------

Q3. How often do you have six or more drinks on one occasion?

0 Never	1 Less than monthly	2 Monthly	3 Weekly	4 Daily or almost daily
----------------	----------------------------	------------------	-----------------	--------------------------------

Do you have a history of any of the following:

Major Anxiety/Depression

Yes ☐ No ☐

Mania

Yes ☐ No ☐

Psychosis/ any other psychological illness

Yes ☐ No ☐

Attention deficit/hyperactivity disorder

Yes ☐ No ☐

Alcohol or substance use problems

Yes ☐ No ☐

Hypertension

Yes ☐ No ☐

Cardiac problems (inc. chest pain/angina)

Yes ☐ No ☐

Liver impairment

Yes ☐ No ☐

Kidney impairment

Yes ☐ No ☐

Epilepsy

Yes ☐ No ☐

Chronic Pain

Yes ☐ No ☐

Asthma

Yes ☐ No ☐

Skin complaints

Yes ☐ No ☐

Severe head injury	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Fits/convulsions	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Loss of consciousness >2 minutes	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Multiple concussions (or any concussion in last 6 weeks)	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Regular giddiness	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Sleep disorders or major sleeping difficulties	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Dyslexia	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Visual impairment	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>

Are you currently taking any medications: (including over-the-counter medications)

Yes ☐ No ☐

For safety, please verify specifically:

Methylphenidate (a drug used for ADHD & narcolepsy) Yes ☐ No ☐

Triazolam (or any benzodiazepine used, for example, in the treatment of insomnia or anxiety) Yes ☐ No ☐

Psychiatric meds for depression (inc. Herbal- hypericum St.Johns Wort), or schizophrenia Yes ☐ No ☐

Phenytoin or other anticonvulsants (any drugs used for epilepsy) Yes ☐ No ☐

Warfarin (anticoagulant, blood thinner) Yes ☐ No ☐

Codeine, fentanyl (or any drugs used for chronic pain) Yes ☐ No ☐

Hormone supplements (testosterone) Yes ☐ No ☐

Daily paracetamol or ibuprophen Yes ☐ No ☐

Medications to treat fungal infections Yes ☐ No ☐

Medications to help you sleep Yes ☐ No ☐

Any other medicines, including any available without a prescription from a pharmacy, supermarket or health food store Yes ☐ No ☐

Any medications over the past week (other than PRN paracetamol) Yes ☐ No ☐

Caffeine use

Q1. How often do you have a drink containing caffeine?

0 Never	1 Monthly or less	2 2-4 times a month	3 2-3 times a week	4 4 or more times a week
----------------	--------------------------	----------------------------	---------------------------	---------------------------------

Q2. How many drinks containing caffeine do you have on a typical day when you have caffeine?

0 1 or 2	1 3 or 4	2 5 or 6	3 7 to 9	4 10 or more
-----------------	-----------------	-----------------	-----------------	---------------------

Q3. How often do you have six or more drinks on one occasion?

Do you have notice any adverse side effects when you drink caffeine? Yes / No

Weight_____ **kg**

Height_____ **cm**

Estimated BMI: _____

Are you left or right handed?

1. In the past 12 months, have you felt that your thoughts were being directly interfered with or controlled by another person?	Yes	<input type="checkbox"/>
	No	<input type="checkbox"/>
1a. Did it come about in a way that any people would find hard to believe, for instance, through telepathy?	Yes	<input type="checkbox"/>
	No	<input type="checkbox"/>
2. In the past 12 months, have you had a feeling that people were too interested in you?	Yes	<input type="checkbox"/>
	No	<input type="checkbox"/>
2a. In the past 12 months, have you had a feeling that things were arranged so as to have a special meaning for you, or even that harm might come to you?	Yes	<input type="checkbox"/>
	No	<input type="checkbox"/>
3. Do you have any special powers that most people lack?	Yes	<input type="checkbox"/>
	No	<input type="checkbox"/>
3a. Do you belong to a group of people who also have these special powers?	Yes	<input type="checkbox"/>
	No	<input type="checkbox"/>
4. Has a doctor ever told you that you may have schizophrenia?	Yes	<input type="checkbox"/>
	No	<input type="checkbox"/>

Appendix F: Experimental Questionnaire

Experimental session questionnaire

Date ____/____/____

Participant ID

1. Check that participant has abstained from alcohol for 24 hours and illicit drug use since completing the screening questionnaire
2. Weight _____ kg
Height _____ cm
BMI _____
3. Have you consumed any medications in the past week (or any prescribed medications since completing the screening questionnaire)?

If yes, please detail:

Medication	Number of occasions	Time since last used	Estimated dose

3.

How many cups of coffee (or any other

caffeinated drinks/products) have you consumed today? _____

If > 0. How many hours since your last caffeinated drink _____ hours

4. Have you had any tobacco or nicotine products today? Yes / No

If yes, how many cigarettes (or nicotine products) have you had today? _____

If yes, How many hours since your last cigarette (nicotine product) _____ hours

5. What have you had to eat today? How long since you last ate something? _____ mins

6. Approximately how many hours sleep did you have last night? _____

These questions are related to your use of alcohol. Remember, any information you provide is completely confidential.

Please circle the most appropriate response

Q1. How often do you have a drink containing alcohol?

0	Never	1	Monthly or less	2	2-4 times a month	3	2-3 times a week	4	4 or more times a week
----------	-------	----------	-----------------	----------	-------------------	----------	------------------	----------	------------------------

Q2. How many drinks containing alcohol do you have on a typical day when you are drinking?

0	1 or 2	1	3 or 4	2	5 or 6	3	7 to 9	4	10 or more
----------	--------	----------	--------	----------	--------	----------	--------	----------	------------

Q3. How often do you have six or more drinks on one occasion?

0	Never	1	Less than monthly	2	Monthly	3	Weekly	4	Daily or almost daily
----------	-------	----------	-------------------	----------	---------	----------	--------	----------	-----------------------

Q4. How often during the last year have you found that you were not able to stop drinking once you had started?

0	Never	1	Less than monthly	2	Monthly	3	Weekly	4	Daily or almost daily
----------	-------	----------	-------------------	----------	---------	----------	--------	----------	-----------------------

Q5. How often during the last year have you failed to do what was normally expected from you because of drinking?

0	Never	1	Less than monthly	2	Monthly	3	Weekly	4	Daily or almost daily
----------	-------	----------	-------------------	----------	---------	----------	--------	----------	-----------------------

Q6. How often during the last year have you needed a first drink in the morning to get yourself going, after a heavy drinking session?

0	Never	1	Less than monthly	2	Monthly	3	Weekly	4	Daily or almost daily
----------	-------	----------	-------------------	----------	---------	----------	--------	----------	-----------------------

Q7. How often during the last year have you had a feeling of guilt or remorse after drinking?

0	Never	1	Less than monthly	2	Monthly	3	Weekly	4	Daily or almost daily
----------	-------	----------	-------------------	----------	---------	----------	--------	----------	-----------------------

Q8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

0	Never	1	Less than monthly	2	Monthly	3	Weekly	4	Daily or almost daily
----------	-------	----------	-------------------	----------	---------	----------	--------	----------	-----------------------

Q9. Have you or someone else been injured as a result of your drinking?

0	No	2	Yes, but not in last year	4	Yes, during the last year
----------	----	----------	---------------------------	----------	---------------------------

Q10. Has a relative or friend or doctor or other health worker been concerned about your drinking or suggested you cut down?

0	No	2	Yes, but not in last year	4	Yes, during the last year
----------	----	----------	---------------------------	----------	---------------------------

Total = (>16)

Well-Being Scale

These questions are related to how you have been feeling over the last 4 weeks. Remember, any information you provide is completely confidential. Please circle the most appropriate response.

In the last 4 weeks, about how often –

1. Did you feel tired out for no good reason?

- None of the time 1
- A little of the time 2
- Some of the time 3
- Most of the time 4
- All of the time 5

2. Did you feel nervous?

- None of the time 1
- A little of the time 2
- Some of the time 3
- Most of the time 4
- All of the time 5

Note: If response 1 chosen, go to Q4

3. Did you feel so nervous that nothing could calm you down?

- None of the time 1
- A little of the time 2
- Some of the time 3
- Most of the time 4
- All of the time 5

4. Did you feel hopeless?

- None of the time 1
- A little of the time 2
- Some of the time 3
- Most of the time 4
- All of the time 5

5. Did you feel restless or fidgety?

- None of the time 1
- A little of the time 2
- Some of the time 3
- Most of the time 4
- All of the time 5

Note: If response 1 chosen, go to Q7

6. Did you feel so restless that you could not sit still?

- None of the time 1
- A little of the time 2
- Some of the time 3
- Most of the time 4
- All of the time 5

7. Did you feel depressed?

- None of the time 1
- A little of the time 2
- Some of the time 3
- Most of the time 4
- All of the time 5

8. Did you feel that everything was an effort?

- None of the time 1
- A little of the time 2
- Some of the time 3
- Most of the time 4
- All of the time 5

9. Did you feel so sad that nothing could cheer you up?

- None of the time 1
- A little of the time 2
- Some of the time 3
- Most of the time 4
- All of the time 5

10. Did you feel worthless?

- None of the time 1
- A little of the time 2
- Some of the time 3
- Most of the time 4
- All of the time 5

Total= (>30)

Please answer each item by checking Y (Yes) or N (No). Answer **all** items even if unsure of your answer. When you have finished, check over each one to make sure you have answered them.

1. People sometimes find me aloof and distant	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2. Have you ever had the sense that some person or force is around you, even though you cannot see anyone?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3. People sometimes comment on my unusual mannerisms and habits	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4. Are you sometimes sure that other people can tell what you are thinking?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
5. Have you ever noticed a common event or object that seemed to be a special sign for you?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
6. Some people think that I am a very bizarre person	Yes <input type="checkbox"/>	No <input type="checkbox"/>
7. I feel I have to be on my guard with friends	Yes <input type="checkbox"/>	No <input type="checkbox"/>
8. Some people find me a bit vague and elusive during a conversation	Yes <input type="checkbox"/>	No <input type="checkbox"/>
9. Do you often pick up hidden threats or put downs from what people say or do?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
10. When shopping do you get the feeling that other people are taking notice of you?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
11. I feel very uncomfortable in social situations involving unfamiliar people	Yes <input type="checkbox"/>	No <input type="checkbox"/>
12. Have you had experiences with astrology, seeing the future, UFOs, ESP, or a sixth sense?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
13. I sometimes use words in unusual ways	Yes <input type="checkbox"/>	No <input type="checkbox"/>
14. Have you found that it is best not to let other people know too much about you?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
15. I tend to keep in the background on social occasions	Yes <input type="checkbox"/>	No <input type="checkbox"/>
16. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
17. Do you often have to keep an eye out to stop people from taking advantage of you?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
18. Do you feel that you are unable to get 'close' to people?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
19. I am an odd, unusual person	Yes <input type="checkbox"/>	No <input type="checkbox"/>
20. I find it hard to communicate clearly what I want to say to people	Yes <input type="checkbox"/>	No <input type="checkbox"/>
21. I feel very uneasy talking to people I do not know well	Yes <input type="checkbox"/>	No <input type="checkbox"/>

22. I tend to keep my feeling to myself

Yes ☐No ☐

Total= **(≥17)**

Weschler Test of Adult Reading

wtar™**WORD CARD**

WESCHLER® TEST OF ADULT READING™

- | | |
|------------------|-------------------|
| 1. again | 26. conscientious |
| 2. address | 27. homily |
| 3. cough | 28. malady |
| 4. preview | 29. subtle |
| 5. although | 30. fecund |
| 6. most | 31. palatable |
| 7. excitement | 32. menagerie |
| 8. know | 33. obfuscate |
| 9. plumb | 34. liaison |
| 10. decorate | 35. exigency |
| 11. fierce | 36. xenophobia |
| 12. knead | 37. ogre |
| 13. aisle | 38. scurrilous |
| 14. vengeance | 39. ethereal |
| 15. prestigious | 40. paradigm |
| 16. wreath | 41. perspicuity |
| 17. gnat | 42. plethora |
| 18. amphitheater | 43. lugubrious |
| 19. lieu | 44. treatise |
| 20. grotesque | 45. dilettante |
| 21. iridescent | 46. vertiginous |
| 22. ballet | 47. ubiquitous |
| 23. equestrian | 48. hyperbole |
| 24. porpoise | 49. insouciant |
| 25. aesthetic | 50. hegemony |

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2 3 4 5 6 7 8 9 10 11 12 A B C D E F

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9 780158 1990187

Profile of Mood States-Short Form

Participant Code:
pre

Test Point:

Below is a list of words that describe feelings people have. Please read each one carefully. Then circle ONE answer to the right, which best describes how you are feeling AT THE MOMENT.

The numbers refer to these phrases:

0=not at all

1=a little

2=moderately

3=quite a bit

4= extremely

- | | |
|--|--|
| <p>1. Tense.....0 1 2 3 4</p> <p>2. Angry.....0 1 2 3 4</p> <p>3. Worn out.....0 1 2 3 4</p> <p>4. Unhappy.....0 1 2 3 4</p> <p>5. Lively.....0 1 2 3 4</p> <p>6. Confused.....0 1 2 3 4</p> <p>7. Peeved.....0 1 2 3 4</p> <p>8. Sad.....0 1 2 3 4</p> <p>9. Active.....0 1 2 3 4</p> <p>10. On Edge.....0 1 2 3 4</p> <p>11. Grouchy.....0 1 2 3 4</p> <p>12. Blue.....0 1 2 3 4</p> <p>13. Energetic..... 0 1 2 3 4</p> <p>14. Hopeless.....0 1 2 3 4</p> <p>15. Uneasy.....0 1 2 3 4</p> <p>16. Restless.....0 1 2 3 4</p> <p>17. Unable to
Concentrate.....0 1 2 3 4</p> <p>18. Fatigued.....0 1 2 3 4</p> <p>19. Annoyed.....0 1 2 3 4</p> | <p>20. Discouraged.....0 1 2 3 4</p> <p>21. Resentful.....0 1 2 3 4</p> <p>22. Nervous.....0 1 2 3 4</p> <p>23. Miserable.....0 1 2 3 4</p> <p>24. Cheerful.....0 1 2 3 4</p> <p>25. Bitter.....0 1 2 3 4</p> <p>26. Exhausted.....0 1 2 3 4</p> <p>27. Anxious.....0 1 2 3 4</p> <p>28. Helpless.....0 1 2 3 4</p> <p>29. Weary.....0 1 2 3 4</p> <p>30. Bewildered.....0 1 2 3 4</p> <p>31. Furious.....0 1 2 3 4</p> <p>32. Full of pep.....0 1 2 3 4</p> <p>33. Worthless.....0 1 2 3 4</p> <p>34. Forgetful.....0 1 2 3 4</p> <p>35. Vigorous.....0 1 2 3 4</p> <p>36. Uncertain about
things.....0 1 2 3 4</p> <p>37. Bushed.....0 1 2 3 4</p> |
|--|--|

Participant Code:
pre

Test Point:

Karolinska Sleepiness Scale

Please circle on the following scale of 1 to 9 how you feel AT THE PRESENT MOMENT:

1. Extremely alert
2. Very alert
3. Alert
4. Rather alert
5. Neither alert nor sleepy
6. Some signs of sleepiness
7. Sleepy, but no effort to keep awake
8. Sleepy, some effort to keep awake
9. Very sleepy, great effort to keep awake, fighting sleep

Visual Analogue Scales of Subjective Performance

Participant number:
pre

Test point:

Please mark on each line at the point which most accurately reflects your level of agreement AT THE MOMENT with the below statement:

1. I feel alert

STRONGLY
AGREE

STRONGLY
DISAGREE

2. I feel that I will be able to perform the attention tasks to the best of my ability

STRONGLY
AGREE

STRONGLY
DISAGREE

3. I do not feel that my driving would be impaired right now

STRONGLY
AGREE

STRONGLY
DISAGREE

4. I feel capable of driving safely right now

STRONGLY
AGREE

STRONGLY
DISAGREE

Visual Analogue Scales of Subjective Drug Effects

Participant number:
pre

Test point:

Please mark on each line at the point which most accurately reflects your level of agreement AT THE MOMENT with the below statement:

1. Strength of drug effect

NO EFFECT _____ VERY STRONG
EFFECT

2. Liking of the drug effect

DISLIKE VERY _____ LIKE VERY
MUCH MUCH

3. Alert level
NOT ALERT

_____ VERY ALERT

4. Intoxication
NOT
INTOXICATED

_____ VERY
INTOXICATED